SmithKline Beecham
Pharmaceuticals

4053 '99 JUL 20 A10:13

16 July 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD, 20852

Re: [Docket No. 99D-0674] Guidance for Industry – *INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products. Chemistry, Manufacturing, and Controls Content and Format*

Dear Madam or Sir:

SmithKline Beecham appreciates the opportunity of providing comments on the draft guidance for industry regarding INDs for Phase 2 and 3 studies of drugs, including specified therapeutic biotechnology-derived products.

PHASE 2 AND PHASE 3 Drug Substance (page 5 - lines 217-219, page 10 - lines 433-436) and Drug Product (page 7 - lines 299-301, page 12 - lines 537-541)

These sections add a requirement for a detailed stability protocol, whereas a summary of the storage conditions and a commitment to monitor concurrently during clinical trials has sufficed in the past.

The following are more specific comments:

Section III.B. Phase 2 Drug Product

Page #	Line #	Comment:
6	226	This line seems to require inclusion of the DMF letter in the Phase 2 IND, whereas the preliminary draft seemed to require only a reference.
6	232	Please define "established name." Only the compendial name was required before.

99D-0674

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1250 S. Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989. Telephone (610) 917 7000. Fax (610) 917 7707.

Section III.B. Phase 2 Drug Product (cont'd)

Page #	Line #	Comment:
6	235-237 & 293-295	This section requires MDI, DPI and nasal spray formulas and devices to be finalized to commercial image for Phase 2. This seems to be a new and burdensome requirement for early phase product.
6	241	We believe it should be clarified that "acceptance requirements for drug substance" applies only to drug substance from a different manufacturer than the drug product sponsor. In addition, this statement implies that this information is required at Phase 1, but it is not included in the Phase 1 IND Guidance.
7	276-286	There is an additional requirement for "reporting changes" to the specification, in addition to simply presenting the proposed specification. This type information did not used to be submitted until the NDA in the specification rationale / development section.
7	303-304	This sentence seems to require submission of all available phase 1 clinical stability data whether it is applicable or not. Please clarify.
7	304	Stress testing (e.g. photostability) on drug product has been added as testing that should be conducted during Phase 2. We believe Industry generally conducts this type of testing on the final dose form during Phase 3 and provides this data in the NDA.

Section IV.B. Phase 3 / Pivotal Study Drug Product

Page #	Line #	Comment:
11	457-458	This sentence seems to suggest that a summary of Phase 1 and 2 formulas be provided. This would be redundant with earlier IND submissions. It is also the type of information that formerly was not required in summary until the NDA.
11	466-469	See note for line 241.

Section IV.B. Phase 3 / Pivotal Study Drug Product (cont'd)

Page #	Line #	Comment:
11	489-490	Industry should not be "locked in" to 1/10 commercial scale for all Phase 3 clinical batches, only the biobatch(es) and qualification batches that must correlate to commercial production.
12	510	The clause "as appropriate" has been deleted from the preliminary draft, making the degradation product statement seem to refer to all cases.
12	523	We suggest changing "manufacturer and supplier" to "manufacturer and/or supplier"
12	532-535	We agree with generating stress and photostability data during Phase 3, however we normally submit this data in the NDA, not a Phase 3 IND amendment.
12	540-541	This protocol description seems to apply more to the qualification stability protocol which may or may not be used for all Phase 3 clinical supplies.
12	541	We recommend changing "profiling" to "testing." Dissolution profiles for stability testing would be appropriate for oral solid modified release products only.
13	548	We object to the requirement for separate stability tables for each storage condition. Development data are usually clearly presentable in one table which includes all storage conditions.
13	558-562	Although this type of information is normally developed during Phase 3, it usually is not submitted until the NDA. It may be discussed at the End of Phase 2 meeting or proposed in the qualification stability protocol, but not necessarily discussed (line 561) in the initial Phase 3 IND where the clinical container closure may not be the proposed commercial system.
15	631-632	Please add a reference to the current guidance for "product": *Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Products* (Feb 1987)?

Comments on Specific Issues:

III. PHASE 2 (page 5, line 193)

We note that "Test results, analytical data, and certificates of analysis (COA) of clinical trial material prepared since the filing of the original IND..." is now requested, whereas in the preliminary draft guidance document the request for batch analysis information was limited to "relevant" lots.

We recommend that the Agency amend statements in the guidance document so as to clarify whether batch analysis information should be provided on all lots used in clinical studies, or whether information on representative clinical lots is sufficient. This should be clarified for both drug substance and drug product at Phase 2 and Phase 3.

We believe that providing specifications and information on relevant, representative lots of drug substance and drug product to be used at each phase of development, and/or following significant manufacturing changes, is sufficient for the Agency to make a determination as to the identity, strength, quality, purity and potency of materials to be used during clinical development. To request batch analysis information on all clinical lots produced places an undue reporting burden on Sponsors during clinical development. It should be noted that batch analysis information on all lots used in clinical studies will be available to the Agency during the Pre-Approval Inspection.

In addition, with particular regard to the "Specified Therapeutic Biotechnology-Derived Products", henceforth "specified biotech products", we note a further discrepancy between Agency statements on the submission of batch analysis information as cited in this draft guidance document and in some letters from the Agency assigning the IND number and product name for new investigational products. We note that many of the specified biotech products fall under the review authority of CBER and are thus assigned a BB-IND number using a form letter which appears to be common to all CBER regulated products (e.g. specified biotech, biologic, vaccine and/or blood products). On page 2 of the CBER form letter, the following statement is included:

> "Prior to use of each new lot of the investigational biologic in clinical trials, please submit the lot number, the results of all tests performed on the lot, and the specifications when established (i.e., the range of acceptable results)."

In this case the reporting requirements for Sponsors are even more burdensome, as multiple and frequent submissions to the IND may be needed to notify each lot of product used during the course of clinical trials.

It is our understanding that the regulatory review process for specified biotech products is to be harmonized more along the lines of the process used for "drug" products, as opposed to "biologic" products. As the current practice for investigational "drug" products is to submit batch analysis on relevant lots used at each phase of clinical studies, we believe the same practice should be applied to the specified therapeutic biotechnology-derived products. Thus, we urge the Agency and CBER to develop a specific form letter to be used for assigning IND numbers and product names for new specified biotech products. Further, we urge that statements pertaining to the provision of batch analysis information in the form letter for specified biotech products be consistent and harmonized with statements in the subject guidance document.

V. PLACEBO (page 13, line 565)
In addition to the information provided during phase 1, data demonstrating the absence of the active ingredient should be provided for phases 2 and 3.

The requirement for testing placebos for the absence of active ingredients should be reconsidered. A review of regulatory requirements for placebos highlights the need to set 'scientifically sound and appropriate' specifications. Identity and strength determinations are specifically prescribed for each active ingredient present in a drug product (CFR 211.165). No regulatory requirements mandate strength determinations (absence of active) or identity of inactive ingredients in a placebo. The draft guideline is essentially adding the requirement to test placebos for the absence of active, a requirement not found in the CFR or the GMPs.

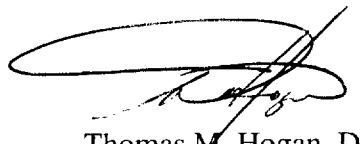
Testing placebos at the time of manufacture for 'absence of active' has been an industry standard which goes hand-in-hand with the common practice of manufacturing placebo dosage forms on an 'as needed basis' to match a particular active medication. It is seemingly logical to test placebos for 'absence of active' since active drug products are tested for presence of drug substance. The flaw in this logic becomes apparent when the manufacture and testing of "multiple use" placebos is considered. Prior to the determination of a commercial image, most investigational drug products are unmarked white round tablets or white opaque capsules which can be matched to "multiple use" placebos. When manufacturing "multiple use" placebos it becomes apparent that the placebo batches need to be tested and released as distinct entities (without reference to an active ingredient).

Therefore a requirement to test placebos for the absence of active leads to the question of which active and why?

There are no requirements to test active drug products to confirm the absence of the other active drug ingredients present in the facility or the active ingredients found in the comparators they will be tested against in the clinic. The fact that the active, comparator and placebo drug products all look alike for blinding purposes is not sufficient reason to require absence of active testing for placebos. If a facilities' manufacturing controls do not prevent the addition of an active ingredient to a placebo dosage form, then they have the same probability of adding an additional active ingredient to an active dosage form. If a facilities' labeling controls are poor enough to allow an active to be dispensed as a placebo, then they have the same probability of dispensing one look alike active for another. Placebos need to be manufactured, tested and packaged in accordance with GMPs, they do not need to be tested for the absence of what they might (or might not) be tested against. We agree that analytical methodology needs to be in place to distinguish between active(s) and placebos when, for example, goods are returned from the clinic with questions as to their identity.

Again, thank you for the opportunity of commenting on these issues. If you have any questions, please contact me at (610) 917-6605.

Sincerely,



Thomas M. Hogan, Director
Chemistry, Manufacturing and Controls
North American Regulatory Affairs
SmithKline Beecham Pharmaceuticals

DHL

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1 From

763302533 | 11R4250

SMITHKLINE BEECHAM

Thomas Hogan

1250 S COLLEGEVILLE RD
COLLEGEVILLE PA

194262990 | (610) 917-6605

2 To

Food and Drug Administration

Rockville, [illegible]

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Signature

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